



A Review on Pathophysiology and Epidemiology of Bovine Papillomatosis

Muhammad Mujeeb Abid¹, Aziz ur Rehman¹, Ishtiaq Ahmed¹, Hafiz Muhammad Zakria², Muhammad Sohaib Aslam³ and Syed Muhammad Adeel Arshad¹

¹Department of Pathobiology, University of Veterinary and Animal Sciences (Jhang Campus); ²College of Animal Science and Technology Northwest A&F University, China; ³Department of Pathobiology Riphah College of Veterinary Science, Riphah International University, Lahore, Pakistan

*Correspondence: aziz.rehman@uvas.edu.pk

ARTICLE INFO

ARTICLE HISTORY: CVJ-25-1216

Received: 06 November 2025
Revised: 13 December 2025
Accepted: 16 December 2025
Published online: 18 December 2025

Key words:

Bovine Papilloma Virus;
Diagnosis;
Transmission;
Tumor

ABSTRACT

Bovine papillomaviruses are small group of double-stranded Deoxyribonucleic acid. Bovine papillomaviruses are oncogenic and epitheliotropic in nature. Bovine papillomaviruses are small non-enveloped dsDNA that have 13 genomes that are fully characterized until now. Many studies revealed that the structure of the Bovine papillomavirus is approximately 3.6 Angstrom resolution and 52-55 nanometer in size. Bovine papillomaviruses are further classified like Xipapilloma virus (BPV 3, 4, 6, 9, 10, 11 and 12), Epsilonpapilloma virus (BPV 5 and 8), Deltapapilloma virus (BPV 1, 2 and 3), and one un-named Papillomavirus is (BPV 7). BPV replicates in upper stratified cells of the epithelial membrane. BPV induces tumors and cancerous growth in epithelial cells. The growth of Bovine papillomaviruses may be exophytic and endophytic in nature. The tumorous and cancerous growth of BPV is a hyperplastic characteristic of epithelial cells of the membrane. BPV causes cancer of the urinary bladder, the tumor of the gastrointestinal tract, and tumors of the mucosal membrane. BPV also causes cancerous and tumorous growth of cutaneous membrane or ulceration and teat papillomatosis. Horizontal and vertical transmission of BPV has been revealed in many review and experimental studies. In this literature transmission of BPV in dairy from animal to animal by direct contact with an infected animal. It also transmits through frictional epithelial contact with animal or blood transfusion and contaminated dairy fomites or fixtures. Usually, the diagnosis of Bovine papillomavirus is through gene amplification of PCR and ELISA test. In the treatment of BPV infection Supportive therapy and Antibiotics are given. But Autogenous vaccine shows ironic results in the quick recovery of BPVs.

To Cite This Article: Abid MM, Rehman AU, Ahmed I, Zakria HM, Aslam MS and Arshad SMA, 2025. A review on pathophysiology and epidemiology of bovine papillomatosis. *Continental Vet J*, 5(2): 140-144. <http://dx.doi.org/10.71081/cvj/2025.059>

INTRODUCTION

Papillomaviruses are oncogenic proteins. Bovine papillomaviruses are a small group of double-stranded Deoxyribonucleic acid and non-enveloped viruses. Bovine papillomaviruses are also called "Fibropapilloma viruses" (Feyisa, 2018). BPVs cause both epithelium and derma ulceration. Bovine papillomaviruses are host specific. Bovine papillomavirus is icosahedral, non-enveloped double-stranded DNA. It is covalently composed of histone core. It is 52-55 nm in diameter and contains L1 and L2 as a major capsid proteins (Prameela and Veena, 2020). During BPV infection in the animal body, the histone core and chromosomal alteration occur. Bovine

papillomaviruses have the potential for various types of oncogenicity (Lunardi et al., 2013). Bovine papillomaviruses are involved in various types of carcinogenesis. Bovine papillomaviruses have the potential to induce benign and malignant tumors. Bovine papillomaviruses are oncogenic and epitheliotropic in nature. In different literature that was revealed Bovine papillomavirus has an oncogenic ability cause tumorous and cancerous growth in the epithelium membrane of different body organs such as Teat papillomatosis, cancerous growth in the upper digestive tract, and urinary bladder cancer (Kale et al., 2019). It penetrates the host body and replicates in stratified cells or the nucleus of the squamous cell epithelium. Bovine papillomavirus has a

typical growth pattern of lesions like cancerous cell growth may be proliferating outward or inverted proliferation of cells (Yang et al., 1985). These growth patterns are the result of the hyperplastic ability of the epithelium. A total of 13 subunits of the Bovine papillomavirus have been characterized until now, which are classified as Epsilonpapilloma virus (BPV 5 and 8), Delta papillomavirus (BPV 1,2 and 3), Xipapilloma virus (3,4,6,9,10,11,12), and one un-named papillomavirus is BPV 7. All these classified types of Bovine papillomavirus have the potential to induce oncogenic activity in the host body. Bovine papilloma virus type 4 most commonly causes sarcoma in the alimentary tract (Campo, 2006). Bovine papilloma virus type 2 causes urinary bladder cancer in animals. Teat papillomatosis is worldwide and a great economic loss to the dairy industry which is caused by mostly BPV type 6. It causes ulceration of the epithelium membrane and rupturing of the milk duct. Further, these two lesions predispose the animal to mastitis. It can also lead to difficult milking of the animal. Bovine Papilloma Virus (1,3,5,7,8,9,10,11) also has the potential to cause teat papillomatosis (Wolf et al., 2010). Many works of literature have shown that Bracken fern has also a great impact on oncogenesis activity. Bracken fern has the potential to increase the clastogenicity of the Bovine papillomavirus. The compound is named Quercetin which is released from bracken fern and mostly degraded in the digestive tract (Tozato et al., 2013). Quercetin induces malignant transformation of bovine cells and has a carcinogenic effect on cultured bovine cells *in vitro*. At the farm level, the Bovine papillomavirus transmits through direct contact with infected animals, contact of abraded skin with infected animals' secretions or frictionally contact, and transmission through mammary secretion, urine, semen, or spermatozoa. Transmission of BPV is also reported through dairy fomites and fixtures. Horizontal and vertical transmission is recorded in the Bovine papillomavirus (Dos Santos et al., 1998). In vertical transmission animal to animal within the same species. In horizontal transmission through natural breeding or mating of the animal with an infected bull or dam. At the dairy farm, it induces warts on the skin of the neck, around the eye, at the forehead, and at the teat and penis of animals. It also induces cancer development in upper GIT, urinary tract carcinoma, penis papillomatosis, and teat papillomatosis (Tozato et al., 2013). The main precaution and control of the Bovine

papillomavirus at the farm level is to separate infected animals from the rest of the herd. Disinfect the place where infected animals reside with a strong disinfectant. In treatment supportive therapy and antibiotic therapy are given. But the autogenous vaccine has ironic results in the quick recovery of animals (Munday, 2014).

Pathogenesis

Bovine papilloma virus proliferates especially in squamous epithelial cells of the skin. Bovine papilloma has a strong affiliation with skin and mucosal cells for proliferating into the body resulting in benign and malignant papilloma (Savini et al., 2019). The bovine papilloma virus enters the body through ingestion, open wound, and other injuries (Fig 1). BPV spreads in the herd through direct or indirect contact of healthy animals with infected animals. Immunosuppressive animals are prone to BPV infection such as long-term sunlight exposure, mutation, malnutrition, and hormonal imbalance are major contributors (Petti et al., 1991). Major histocompatibility complex Class I presents antigenic peptides of the viral genome to effector T-cells and plays a vital role in immune surveillance of body. Peptides of B-micro-globulin and chaperones are associated with MHC-I in the endoplasmic reticulum (Shanshol and Ahmed, 2021). At this stage, B-micro-globulin and chaperones are loaded into MHC-I heavy chains in optimum pH conditions. The complex of MHC-I and chaperones which are made up of endoplasmic reticulum is further transported to Golgi apparatus where dissociation of the Major histocompatibility complex from chaperones occurs to the plasma membrane for conceding by T-cells later (Roperto et al., 2011).

E5 cells prevent the transportation of MHC-I to the cell surface by dissociation in Golgi apparatus. E5 cell causes down regulation of MHC-I at different levels, followed by impaired transportation of MHC-I to cell surface also reduced transcription of MHC-I heavy chains and lowers the trend of MHC-I proteins or peptides (Silva, 2011). There is still scarcity of satisfactory information about E5 induces the degradation of major histocompatibility class I, but recent studies showed that E5 induces alkalization of Golgi apparatus for dissociation of MHC-I. by successful down regulation of MHC-I, E5 helps to avoid host body from immune surveillance for any foreign agent and thus initiate the successful BPV infection in host body as shown in fig 2 (Meng et al., 2021).

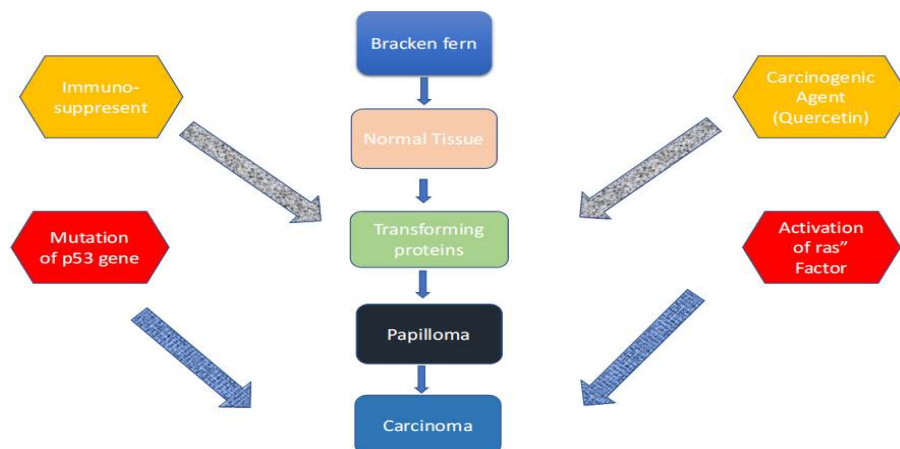


Fig 1: Schematic diagram showing bracken fern (Carcinogenic agent) provokes normal tissue or cell into producing transforming proteins which end point production carcinoma mass.

Normal Function of MHC-1

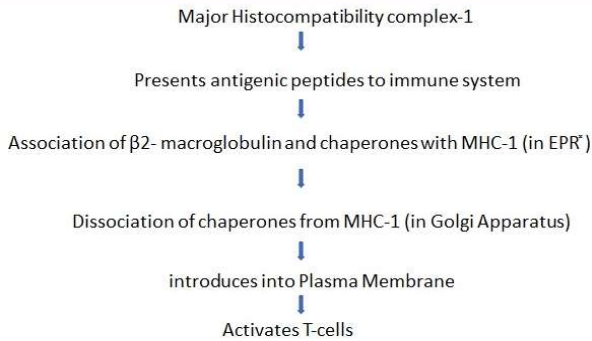


Fig 2: Flow chart represents pathogenesis of bovine papilloma virus at cellular level, E5 cells activation and causes down-degradation of MHC-I.

Transmission

Bovine papillomavirus is host or species-specific but cross-species transmission or diseases are also documented (Yagui et al., 2008). Bovine papillomavirus transmission is in much literature is still a question or not understood completely. In this document, we discuss the transmission of Bovine papillomaviruses between the same species or intra-species (Freitas et al., 2003). The prime object of this study is how transmission occurs at the herd or farm level. Until now, very little knowledge is present about the transmission of Bovine papillomaviruses among animals. Animals that are housed in confined places are more susceptible to getting Bovine papillomavirus (Rombaldi et al., 2008). Many studies have shown the transmission of Bovine papillomaviruses through direct or indirect contact, vertical and horizontal transmission. Recent works of literature documented that transmission of BPV can happen through body fluids (mammary secretions, uterine secretions, urine, seminal fluids), exfoliated dermis cells, and non-epithelial cells (Rombaldi et al., 2008). Arthropods also play a great vector role in the transmission of Bovine papillomaviruses. Previously introduction has been documented that the Bovine papillomavirus is present in the peripheral blood system. Most Bovine papillomavirus type 2 has a high titer in lymphocytes. Recent insights that lymphocytes are suitable and latent sites for Bovine papilloma viral infection (Dos Santos et al., 1998). At the farm level transmission of Bovine papillomavirus through blood transfusion due to the presence of BPV in lymphocytes. BPV infection has a high number of mononuclear cells present in periphery blood in association with inflammatory responses in mammary glands. Bovine papillomavirus transmits through direct or indirect contact of a healthy animal with Urine, mammary secretions, uterine secretions of an infected animal (Sedlacek et al., 1989). BPV also can transmit through dairy fomites and fixtures. BPV transmits through frictionally and living contact with infected animals as shown in fig 3. Lymphocytes are not providing the latent site for Bovine papilloma viral infection but also play a vital role in vector transmission of BPV. Many research documents revealed that, if we give the lymphocyte-BPV injection to an animal intramuscularly and contaminated epidermis cells introduce to healthy epidermis cells can transmit Bovine papillomavirus. Recent insights showed that the Bovine

papillomavirus of epidermis cells in bovine and bovine papillomavirus in epidermis cells of the horse correlates with the transmission. BPV in equines induces *equine sarcoid* which transmits through direct contact or flies to play a vector role to transmit this BPV from bovine cells to equine (Lunardi et al., 2013). Bovine Papillomaviruses also have cross-species transmission. BPV has zoonotic aspects also by the transmission of Papillomaviruses in humans (HPV). Bovine papillomaviruses have a great diversity of transmission in different species like close related animal Buffalo (Lawson et al., 2018). Bovine papillomavirus causes equine sarcoid in equine, fibro-sarcoma in rodents, and feline sarcoid (FeSarPV). BPV can also transmit infection in domesticated or wild animals. Most Cross-species infection is driven by vector-borne transmission. BPV-infected animal has potential to transmit disease inter-species or intra-species (Brandt et al., 2008).

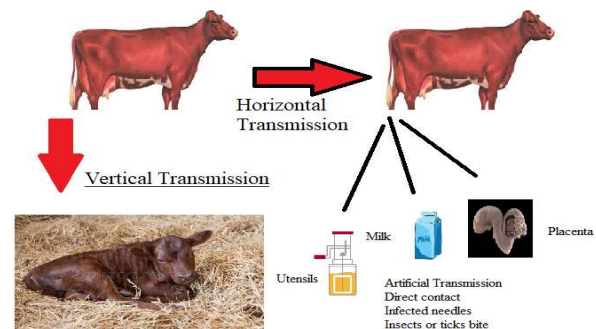


Fig 3: Schematic representation of horizontal, vertical and artificial transmission of bovine papilloma virus.

Epidemiology

Bovine papilloma virus has been predominately present in cattle worldwide. Bovine papilloma virus cases have been reported in Europe, Middle East Asia, Oceania, and America. (Schmitt et al. 2010) has been reported different types of BPV -1, 6, 8 and 10 from the German cowshed. Many cases in Japan have observed that BPV-06 was the causative agent of benign teat tumors in cattle (Maeda et al. 2007). In other exploratory study has shown that BPV-1, 3, 5, and 6 were detected in papilloma sarcoma specimens (Ogawa et al. 2004). (Singh et al. 2009) has been reported bovine cutaneous warts and isolated BPV type 1 and 2 from papilloma specimens. This study also documented that BPV-10 causes teat warts or papilloma in cattle in India. (Shanshol and Ahmed 2021) was conducted a study during the BPV outbreak in Iraq (2020), evaluated the pathological and molecular detection of BPV. According to this study case prevalence ratio in female animals was 70.69% and in male animals 29.31%. papilloma of different locations mentioned in this study in which the most prominent areas of papilloma were the head (22.41%), neck (17.24%), mouth (12.06%), and chest (13.79%). In Egypt n=308 cutaneous warts from head, neck, and mouth were collected for PCR detection of BPV, and phylogenetic analysis confirmed total 84.6% positive case ratio for BPV (El-Tholoth et al. 2020). Cases have been reported at 50% with BPV case ratio in UK, and multiplex BPV genotyping PCR confirmed and documented the prevalence of BPV-1, 2 and 11 in mouth and teat warts (Schmitt et al. 2010).

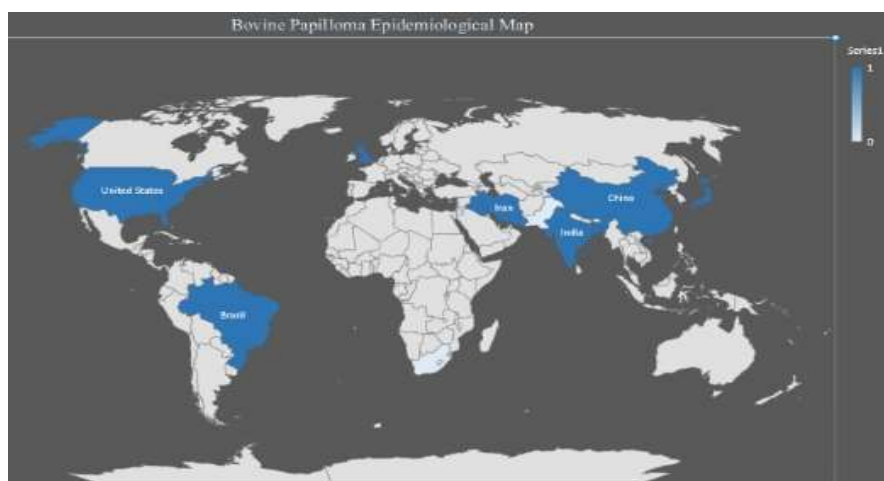


Fig 4: ArcGIS map representation of epidemiological prevalence of bovine papilloma virus.

****1 (Dark Blue)** = Country with High BPV Prevalence.

****0 (Light Blue)** = Country with Low BPV Prevalence.

Treatment

Bovine papillomatosis is an emerging viral disease in the dairy industry nowadays. It is mostly seen in young calves, heifers, and adult milking cows. Mostly at the farm level, the Bovine papillomavirus induces cutaneous papillomatosis in animals, in which warts produce around the neck, eye, abdomen, and teats of animals (Budianto Panjaitan et al., 2021). Warts around the abdomen of an animal body in Bovine papillomavirus are like cauliflower-like appearance. BPV is a self-limiting disease, it regresses spontaneously. It is not a long last disease, but it can persist due to multifactor environmental influence, genetic disorders, and metabolic disorders in an animal body. These factors play a vital role in the persistence of the bovine papillomavirus. Bovine papillomavirus can also produce carcinomas, fibromas, gastric and urinary bladder cancer if BPV long lasts in the body of an animal. BPV has oncogenic and carcinogenic effects on the host body. BPV introduces into the body by multiple exposures to the virus in lesion epithelium. It replicates in stratified cells and induces the formation of warts in the host body as stated above. In this literature, we discuss effectively and routinely practices to control and prevent the bovine papillomavirus. Prevention of BPV is the separation of infected animals from the rest of the herd and clean the bedding of infected animals on the farm with strong disinfectants or sun rays, sprinkle of calcium carbonate is also an effective measure to control it. The most effective and suitable method of treatment for BPV is an *autogenous vaccine* (Kale et al., 2019). In this review study, evaluate how to prepare a non-purified but effective autogenous vaccine of BPV at the farm level as per authentic laboratory instructions. Separate the infected animal and clean the warts area with antiseptic or normal saline (0.9 NaCl). Manually excision of warts and make a suspension in 10% phosphate buffer solution. Manually grind the suspension and keep it at room temperature (25 degrees C). Add 0.04ml of 40% formaldehyde in the solution and centrifuge it at 3000 rpm for 30 minutes, after this procedure filter the solution with a Maslin cloth. Now clear supernatant of solution pours into a test tube and add *procaine penicillin* (5ml) and streptomycin (10ml) for

inhibiting bacterial or fungi growth in the vaccine. Injected 5ml I/c or 10mls s/c once in 3 days (Sawchuk et al., 1989). On day 60th warts of the vaccinated animal body completely vanished. In this literature review, usage of some anthelmintic drugs is also documented in the treatment of bovine papillomavirus infection in which ivermectin is injected at day 1 and repeated dose at day 8. Steroids like dexamethasone or prednisolone 10ml are also injected with anthelmintic drugs (Feyisa, 2018). Now amazing technology for the removal of warts has occurred. Nowadays many cooperative dairy sectors practice the removal of warts by Carbon dioxide vapor laser technique. First, measure the diameter of the wart and clean the area with an antiseptic solution. Anesthetized the area around warts in a ring shape with an anesthesia agent (1% lidocaine or 0.025% bupivacaine) for reduction of pain in animals. Use dual focusing or fractional carbon dioxide laser on the wart. It produces thermal energy in the shape of the beams with a speed of 3mm/sec and an intensity of 1270W/cm² as documented by (Ugochukwu et al., 2019).

DECLARATION

Funding: Not Available.

Acknowledgement: None.

Conflicts of Interest: All authors of the manuscript declare that they have no financial or personal interests.

Data Availability: Raw data may be available on request.

Ethical Statement: This is a review article and no animals were involved.

Authors Contribution: All the authors participated equally.

Generative AI Statement: The authors declare that no Gen AI/DeepSeek was used in the writing/creation of this manuscript.

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